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(54) Title: PHARMACEUTICAL COMPOSITION FOR OPHTHALMIC USE COMPRISING A WATER SOLUBLE ACID ADDITION SALT OF IBOPAMINE

(57) Abstract

The solution is buffered at pH 4.5 and comprises from 0.1 to 0.5 parts by weight of hydroxy propyl methyl cellulose for each part by weight of a water soluble pharmaceutically acceptable acid addition salt of ibopamine.

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"Pharmaceutical composition for ophthalmic use comprising a water soluble acid addition salt of ibopamine"

DESCRIPTION

The present invention relates to a pharmaceutical composition for ophthalmic use comprising a water soluble pharmaceutically acceptable acid addition salt of ibopamine.

More particularly, the present invention relates to a pharmaceutical aqueous solution for ophthalmic use which is buffered at pH 4.5 and comprises both a water soluble pharmaceutically acceptable acid addition salt of ibopamine and hydroxy propyl methyl cellulose.

It is well known that ibopamine, i.e. epinine 3,4-O-diisobutyrate, is endowed with mydriatic activity (WO 86/03970).

During intensive studies on the properties of aqueous solutions for ophthalmic use comprising a water soluble pharmaceutically acceptable acid addition salt of ibopamine, it has been found that the aqueous solutions of said ibopamine salts such as, for example, hydrochloride, are stable at room temperature for seven days. At lower temperatures the stability of said solutions is slightly greater; in fact, the stability at ± 3°C is of 15 days.

It has now been found that the stability at room temperature is substantially improved when said solutions are buffered at pH 4.5.

Actually, ibopamine titer in aqueous solutions of ibopamine hydrochloride buffered at pH 4.5 remains substantially unchanged for 20-25 days at room temperature and this period of

time is sufficient to allow administration of the whole content of a conventional container (i.e. a 5-10 ml small bottle).

Table I

1% solution of ibopamine buffered at different pH

Stability data

Room Temperature

| | 1 day | 7 days | 15 days | 20 days |
|---|---|---|---|---|
| pH 4.5 | 100% | 98% | 95% | 90% |
| 6 | 95% | 79% | 68% | --- |
| 7 | 80% | 48% | 35% | --- |

Table II

2% solution of ibopamine buffered at pH 4.5

Stability data

Room Temperature

| | 1 day | 7 days | 15 days | 20 days |
|---|---|---|---|---|
| pH 4.5 | 100% | 98% | 95% | 91% |

In addition, it has been found that the bioavailability of an aqueous solution of a water soluble salt of ibopamine doubles when said solution contains hydroxy propyl methyl cellulose (also sold under the trademark Methocel - Merck Index X ed., pag. 706, No. 4764).

The evaluation of the mydriatic effect after administration of 1 drop of 1% ibopamine collyrium containing hydroxy propyl methyl cellulose vs. 2% ibopamine collyrium without hydroxy propyl methyl cellulose has been carried out on 13 patients (6 female and 7 male) whose mean age was 50.2 ± 2.7 years; each patient has been treated (single dose) with both collyria at an interval of 7 days between a treatment and the next one. Posology was 1 drop in the right eye; left eye was was not treated (control).

Pupil diameter was measured with a biomicroscope immediately before (zero time) and 30, 60, and 120 minutes after each treatment.

Local tolerability was evaluated on the basis of the following parameters: appearance and degree of burnings and/or of conjunctival hyperemia.

Table III shows the mean results ± e.s.. Maximum pupil dilatation was obtained after 30-60 minutes on the avarage. Meanwhile, the diameter of left eye remained substantially unchanged.

Statistical analysis proves that the two treatments are not significantly different.

Table III

Modification of pupil diameter (mm) after treatment with 1% ibopamine collyrium containing 0.3% of hydroxy propyl methyl cellulose (HPMC) vs. 2% ibopamine collyrium without HPMC.

Mean ± e.s. in 13 patients

| Treatment | Time(minutes) | | | |
|---|---|---|---|---|
| | 0 | 30 | 60 | 120 |
| 1% ibomamine + HPMC | 2.39 ± 0.04 | 6.55 ± 0.52 | 7.90 ± 0.49 | 6.79 ± 0.39 |
| 2% ibopamine | 2.31 ± 0.05 | 6.77 ± 0.57 | 7.93 ± 0.52 | 6.80 ± 0.42 |

Therefore, this invention relates to a pharmaceutical aqueous solution for ophthalmic use comprising a water soluble pharmaceutically acceptable acid addition salt of ibopamine, characterized in that said solution is buffered at pH 4.5 and comprises from 0.1 to 0.5 parts by weight of hydroxy propyl

methyl cellulose for each part by weight of said ibopamine salt.

The solution of this invention will preferably comprise from 0.5 to 5 parts (w/v) of a water soluble pharmaceutically acceptable acid addition salt of ibopamine; even more preferably they will contain from 1 to 2 parts (w/v) of said ibopamine salt.

Ibopamine hydrochloride is a typical example of a water soluble acid addition salt suitable for preparing the solution of this invention.

The solution of this invention may also comprise from 0.001 to 0.2 parts (w/v) of benzalkonium chloride and from 0.2 to 4 parts (w/v) of mannitol. Furthermore, the solution of this invention may comprise from 0.01 to 0.09 parts (w/v) of EDTA.

Suitable compounds for buffering the solution of this invention are, for example, citric acid and disodium phosphate.

The pharmaceutical composition according to the present invention may comprise other excipients suitable for ophthalmic administration and may be prepared according to conventional methods.

Examples of known containers which may be used in connection with the solution of this invention are those enabling the instant preparation of a sterile solution by a patient in need thereof. A typical package will comprise (i) a small bottle containing a sterile powder or a freeze dried powder, (ii) a vial containing a sterile solvent and (iii) a sterile dropper adapted to fit with said bottle after addition of the solvent to the powder.

A combination of a cap reservoir, dropper and bottle may also be used as described in EP-A-217,425.

This invention relates also to a process for preparing a pharmaceutical composition for ophthalmic use, characterized in that said process comprises distributing a sterile dried water soluble pharmaceutically acceptable acid addition salt of ibopamine in a first sterile container and a substantially aqueous sterile solution having pH 4.5 and comprising from 0.1 to 0.5 parts by weight of hydroxy propyl methyl cellulose for each part by weight of said ibopamine salt in a second sterile container, said sterile solution being adapt to form a mydriatic solution when added to said ibopamine salt before administration to a patient in need of a mydriatic effect.

The following compositions and examples are intended to illustrate the present invention without, however, limiting it in any way.

Composition 1

| | |
|---|---|
| Ibopamine hydrochloride | 1.000 g |
| Citric acid monohydrate | 0.526 g |
| Dibasic sodium phosphate dodecahydrate | 1.376 g |
| Methocel F4M Premium EP (registered trademark) | 0.300 g |
| Benzalkonium chloride | 0.010 g |
| Mannitol | 2.000 g |
| Sterile water | q.s. to 100 ml |

Composition 2

| | |
|---|---|
| Ibopamine hydrochloride | 1.000 g |
| Citric acid monohydrate | 0.520 g |
| Disodium phosphate dodecahydrate | 1.380 g |
| Methocel F4M Premium EP (registered trademark) | 0.300 g |
| Benzalkonium chloride | 0.010 g |
| Mannitol | 2.000 g |
| EDTA | 0.050 g |

| | |
|---|---|
| Sterile water | q.s. to 100 ml |

Composition 3

| | |
|---|---|
| Ibopamine hydrochloride | 2.000 g |
| Citric acid monohydrate | 0.351 g |
| Dibasic sodium phosphate dodecahydrate | 0.920 g |
| Methocel F4M Premium EP (registered trademark) | 0.300 g |
| Benzalkonium chloride | 0.010 g |
| Mannitol | 1.333 g |
| Sterile water | q.s. to 100 ml |

Example 1

| A) Freeze-dried product | composition for 1 vial | composition for 1,000 vials |
|---|---|---|
| Ibopamine hydrochloride | mg 60 | g 60 |
| Mannitol | mg 120 | g 120 |
| Water for injection | q.s. to ml 1.5 | l 1.5 |

| B) Solvent | | |
|---|---|---|
| Hydroxy propyl methyl cellulose | mg 18 | g 18 |
| Citric acid monohydrate | mg 31.6 | g 31.6 |
| Disodium hydrogen phosphate dodecahydrate | mg 82.8 | g 82.8 |
| Benzalkonium chloride | mg 0.6 | g 0.6 |
| Water for injection | q.s. to ml 6 | l 6 |

Ibopamine hydrochloride (60 g) and mannitol (120 g) have been dissolved under stirring in 1,500 ml of water for injection. The solution has been filtered in sterile conditions through a sterile membrane (porosity, 0.2 $\mu$). In a sterile room, the solution has been distributed in 1,000 sterile vials and these vials have been freeze-dried at the following

conditions:

- freezing, plates were cooled at -50°C for 5 hours;
- primary drying, reduced pressure (about 50 µBar) for 1 hour; plates were then warmed from -50°C to +20°C in 21 hours (temperature gradient, 0.05°C/min.)
- secondary drying, vials have been maintained at +20°C for five hours, at the end of the treatment the residual pressure was of about 10-15 µBar.

Finally, the vials have been plugged in sterile condidions with sterile closures.

The preparation of vials containing the solvent has been carried out as follows: hydroxy propyl methyl cellulose has been dispersed in 2 l of boiling water (for injection). Citric acid monohydrate, disodium hydrogen phosphate dodecahydrate and benzalkonium chloride have been added. The remaining water for injection (4 l) has been cooled and added under stirring and cooling. The clear and viscous solution has been filtered in sterile conditions through a sterile membrane (porosity, 0.2 µ). This solution has been then distributed, in a sterile room, in 1,000 sterile vials which have been closed with sterile closures. Finally the vials have been sterilized in a autoclave at 121°C for 21 minutes.

Example 2

| A) Freeze-dried product | composition for 1 vial | composition for 1,000 vials |
|---|---|---|
| Ibopamine hydrochloride | mg 120 | g 120 |
| Mannitol | mg 80 | g 80 |
| Water for injection | q.s. to ml 2 | l 2 |

B) Solvent

| | | | | | |
|---|---|---|---|---|---|
| Hydroxy propyl methyl cellulose | | mg | 18 | g | 18 |
| Citric acid monohydrate | | mg | 21.06 | g | 21.06 |
| Disodium hydrogen phosphate dodecahydrate | | mg | 55.2 | g | 55.2 |
| Benzalkonium chloride | | mg | 0.6 | g | 0.6 |
| Water for injection | q.s. to | ml | 6 | l | 6 |

The freeze-dried product (A) and the solvent (B) have been prepared in a way similar to that described in example 1.

CLAIMS

1. A pharmaceutical aqueous solution for ophthalmic use comprising a water soluble pharmaceutically acceptable acid addition salt of ibopamine, characterized in that said solution is buffered at pH 4.5 and comprises from 0.1 to 0.5 parts by weight of hydroxy propyl methyl cellulose for each part by weight of said ibopamine salt.

2. A solution according to claim 1, characterized in that Methocel 4M Premium EP is used as hydroxy propyl methyl cellulose.

3. A solution according to any of the preceding claims 1 and 2, characterized in that said solution comprises from 0.001 to 0.02 parts (w/v) of benzalkonium chloride.

4. A solution according to any of the preceding claims from 1 to 3, characterized in that said solution comprises from 0.2 to 4 parts (w/v) of mannitol.

5. A solution according to any of the preceding claims from 1 to 4, characterized in that said solution comprises from 0.01 to 0.09 parts (w/v) of EDTA.

6. A solution according to any of the preceding claims from 1 to 5, characterized in that ibopamine hydrochloride is the water soluble pharmaceutically acceptable acid addition salt of ibopamine.

7. A solution according to claim 6, characterized in that 100 ml of said solution comprise from 0.5 to 5 g of ibopamine hydrochloride.

8. A solution according to claim 7, characterized in that 100 ml of said solution comprise from 1 to 2 g of ibopamine hydrochloride.

9. A solution according to claim 8, characterized in that 100 ml of said solution comprise 0.3 g of Methocel F 4M Premium EP.

10. A solution according to claim 8, characterized in that 100 ml of said solution comprise 0.05 g of EDTA.

11. A solution according to claim 8, characterized in that 100 ml of said solution comprise 0.01 g of benzalkonium chloride.

12. A solution according to claim 8, characterized in that 100 ml of said solution comprise 2 g of mannitol.

13. A solution according to any of the preceding claims from 1 to 12, characterized in that said solution is instantly preparable by a patient in need thereof.

14. A process for preparing a pharmaceutical composition for ophthalmic use, characterized in that said process comprises distributing a sterile dried water soluble pharmaceutically acceptable acid addition salt of ibopamine in a first sterile container and a substantially aqueous sterile solution having pH 4.5 and comprising from 0.1 to 0.5 parts by weight of hydroxy propyl methyl cellulose for each part by weight of said ibopamine salt in a second sterile container, said sterile solution being adapt to form a mydriatic solution when added to said ibopamine salt before administration to a patient in need of a mydriatic effect.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 89/01304

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 31/22, A 61 K 9/06, A 61 K 47/38

## II. FIELDS SEARCHED

Minimum Documentation Searched [7]

| Classification System | Classification Symbols |
|---|---|
| IPC[5] | A 61 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

| Category [10] | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| X | WO, A, 86/03970 (SIMES) 17 July 1986 see claims; page 6, lines 3-12,21-25; page 7, lines 1-3; page 7, examples cited in the application | 1,3-8,10-13 |

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## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
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| 5th February 1990 | 23.02.90 |
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| EUROPEAN PATENT OFFICE | T.K. WILLIS |

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 8901304 SA 32373

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/02/90
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO-A- 8603970 | 17-07-86 | EP-A,B 0205606 | 30-12-86 |
| | | JP-T- 63502270 | 01-09-88 |
| | | US-A- 4764530 | 16-08-88 |